IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent of:

Raymond ANDERSEN et al.

Patent Number: US 6, 870,028 B1 **ATTN: Certificates of Correction**

Issued: March 22, 2005

For: BIOLOGICALLY ACTIVE PEPTIDES AND COMPOSITIONS, THEIR USE

REQUEST FOR CERTIFICATE OF CORRECTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Date: August 20, 2008

Sir:

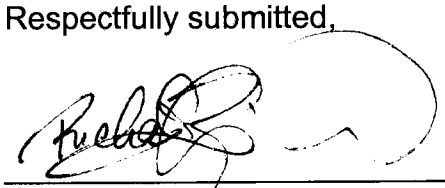
The undersigned respectfully requests that a Certificate of Correction be issued for the above-identified patent as indicated on the attached Form PTO 1050.

REMARKS

This request is being made in order to correct an error noted in Claim 1, Formula 1 of the above-identified patent. In support of this request, enclosed is a copy of the title page of the Letters Patent document.

Since the error in the patent appear to be those of the U.S. Patent and Trademark Office, it is respectfully submitted that no fee is required. However, in the event that any fees are due with respect to this paper, please charge Deposit Account Number 01-2300, referencing Attorney Docket Number 108281-00001.

Respectfully submitted,



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Enclosure(s): Form PTO 1050
Title Page of Letters Patent Document (copy)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.: 6,870,028 B1

DATED : March 22, 2005

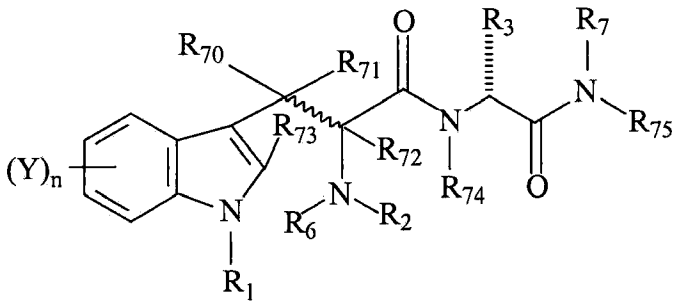
INVENTOR(S): Raymond Andersen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE CLAIMS:

Please amend Claim 1 as follows:

Claim 1, Formula 1, should read:



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Patent No. 6,870 028 B1

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FORM PTO 1050 (REV. 3-82)

US006870028B1

(12) **United States Patent**
Andersen et al.

(10) **Patent No.: US 6,870,028 B1**
(45) **Date of Patent: Mar. 22, 2005**

(54) **BIOLOGICALLY ACTIVE PEPTIDES AND COMPOSITIONS, THEIR USE**

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(73) Assignees: **University of British Columbia**, Vancouver (CA); **University of Alberta**, Edmonton (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 271 days.

(21) Appl. No.: **09/593,417**

(22) Filed: **Jun. 14, 2000**

Related U.S. Application Data

(62) Division of application No. 08/930,584, filed as application No. PCT/GB96/00942 on Apr. 22, 1996, now Pat. No. 6,153,590.

(30) **Foreign Application Priority Data**

Apr. 20, 1995 (GB) 9508195

(51) **Int. Cl.**[7] **C07K 5/08**

(52) **U.S. Cl.** **530/331**; 514/18; 514/19; 548/496

(58) **Field of Search** 514/18, 19; 530/331; 548/496

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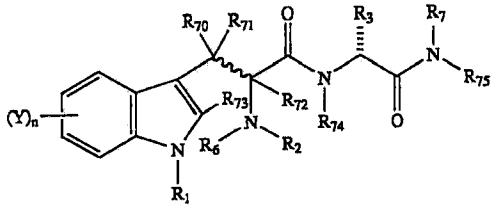
(74) *Attorney, Agent, or Firm*—Arent Fox PLLC

(57) **ABSTRACT**

This invention relates to derivatives of hemiasterlin or Geodiamolide G having anti-mitotic activities and useful in treating cancer. These derivatives are represented by general formula I,

I

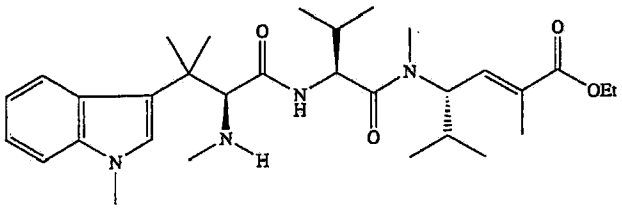


wherein Y, n, R_1, R_2, R_3, R_6, R_7, R_{70}, R_{71}, R_{72}, R_{74}, and R_{75} are as defined in the specification.

13 Claims, 1 Drawing Sheet

TABLE 4-continued

	IC_{50} Values (μg/ml)				
	P388	U373	HEY	MCF7	cell mitosis
Totally Synthetic Analogue				0.1	



3. Compounds described herein were comparatively tested for their antimitotic activity against human mammary carcinoma MCF7 cells.

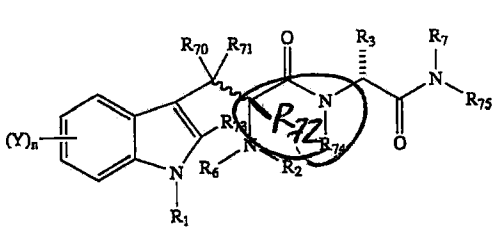
MCF7 cells were grown as a monolayer in RPMI supplemented with 15% fetal calf serum and antibiotics at 37° C. in humidified 10% CO_2. All compounds were dissolved in dimethyl sulfoxide except for vinblastine (a known drug) which was a 1 mg/ml solution in physiological saline. Exponentially growing MCF7 cells were treated with different drug concentrations for 20 h, prepared for chromosome spreads, and the percentage of mitotic cells determined by fluorescence microscopy. The results are shown in FIGS. 1 and 2. Hemiasterlin, Hemiasterlin A and modified compounds were very potent antimitotic agents, with IC_{50} values of 0.3 nM and 3 nM respectively. Hemiasterlin and Hemiasterlin A were more potent than Taxol, Vinblastine and Nocodazole (all known drugs).

The effect of Hemiasterlin and Hemiasterlin A on the morphology of their mitotic spindles was examined by indirect immunofluorescence using a monoclonal antibody to β-tubulin and the distribution of their chromosomes using the fluorescent DNA dye bisbenzimide. In the presence of hemiasterlin A at 2 nM no completely normal spindles were seen. Some cells showed relatively minor abnormalities in which a bipolar spindle was present but the astral microtubules were considerably longer than normal and the chromosomes were not completely confined to the metaphase plate. Most commonly cells had multiple asters, and the chromosomes were distributed in a spherical mass. Half-maximal concentrations of taxol, vinblastine and nocodazole produced the same types of abnormal spindle as hemiasterlin A. Hemiasterlin A at 10 nM, the lowest concentration causing maximal mitotic arrest in MCF7 cells, caused microtubule depolymerisation in mitotic cells. This was also the case for high concentrations of vinblastine and nocodazole. Taxol at high concentrations had a quite different effect, causing bundling of cytoplasmic microtubules in interphase cells and very dense multiple asters in mitotic cells.

These results show that Hemiasterlins cause mitotic arrest and produce abnormal mitotic spindles. They can be used in lieu of other antimitotic drugs in procedures that require blocking cells in mitosis, such as the preparation of mitotic spreads for karyotype analysis. They can also be used to probe microtubule function in mitotic cells.

What is claimed is:

1. A compound of general formula I



I

wherein:

R_1 and R_{70} independently represent a hydrogen atom or an optionally substituted alkyl or acyl group with the proviso that when R_{71} is hydrogen as hereinafter described, R_{70} is not hydrogen;

R_2 represents a hydrogen atom, an alkyl or benzoyl group or an alkyl group substituted with one or more halo, nitro, cyano, alkoxy, hydroxy, amino, alkylamino, sulphinyl, alkylsulphinyl, sulphonyl, alkylsulphonyl, amido, alkylamido, alkoxycarbonyl, haloalkoxycarbonyl or haloalkyl groups;

R_{73} represents a hydrogen atom or an optional substituent;

Y represents an optional substituent;

n represents 0, 1, 2, 3, or 4;

R_3 represents a hydrogen atom, or an optionally substituted alkyl group;

R_{74} represents a hydrogen atom, a hydroxy group or an optionally substituted alkyl or acyl group;

R_7 represents a hydrogen atom or an alkyl group;

R_{75} represents an optionally substituted alkyl group or —Q'—C(O)X, wherein

Q' is an optionally substituted —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$—, —CH_2CH=CH—, —CH_2C≡C—, or phenylene, X is —OR_8, —SR_8, or —NR_9R_{10}, and R_8, R_9 and R_{10} independently represent a hydrogen atom or an optionally substituted alkyl group; and

i) R_6 represents a hydrogen atom, an alkyl or benzoyl group or an alkyl group substituted with one or more halo, nitro, cyano, alkoxy, hydroxy, amino, alkylamino, sulphinyl, alkylsulphinyl, sulphonyl, alkylsulphonyl, amido, alkylamido, alkoxycarbonyl, haloalkoxycarbonyl or haloalkyl groups; R_{71} represents a hydrogen atom or an optionally substituted alkyl or acyl group; and R_{72} represents a hydrogen atom; or